# REMARKS

Reconsideration and allowance of the captioned patent application are respectfully requested. The present invention relates to substituted quinazolines and pyrido[3,2-d] pyrimidines, as well as pharmaceutically acceptable salts thereof, as well as pharmaceutical compositions and methods of use.

Claims 1-10 and 14-16 were previously in the case. Claims 11-13 were previously cancelled. Claims 6 and 10 are cancelled herein. Claims 1, 7, 8 and 9 are amended herein. Claims presently in the case are claims 1-5, 7-9 and 14-16.

The Examiner required restriction between the following patentably distinct groups of claims:

I: Claims 1-5, 7, 9, 10 and 14-16 drawn to compounds of formula I (and I-1) in which X equals CH, compositions and methods of treatment therewith;

II: Claims 1-4, 6, 8-10 and 14-16 drawn to compounds of formula I (and I-2) in which X equals N, compositions and methods of treatment therewith.

Applicants confirm election of group I, in which X represents CH with traverse.

Claims that fall within group I include claims 1-5, 7-9 and 14-16, as these claims have been amended. Applicants respectfully traverse the restriction requirement as set forth below. The Examiner has not demonstrated that a significant burden will be placed upon the Examiner if the groups are combined and a single search is conducted. Significant time and expense can be saved on the part of the Applicants if the Examiner combines the groups and examines both groups in a single application.

Moreover, the PCT Unity of Invention rules apply in the present case, since it is a national phase application filed under 35 USC § 371. The Examiner's allegation of lack of unity is not consistent with the PCT prosecution, where no unity of invention objection was made. Therefore,

upon making a determination that the group elected is patentable, the Examiner should broaden the search to include the subject matter of group II.

The Examiner's comments regarding lack of a single general inventive comment are urged to be incorrect. The single general inventive concept is embodied in generic structure (I), a bicyclic 10-membered heteroaromatic ring system containing a fused pyrimidine ring that is substituted with a ring or ring system attached to an amino group at position 4, and a group attached through an oxygen or sulfur at position 6. The compounds are glucokinase activators and are thus useful for the treatment of diabetes, obesity and related conditions.

The comment regarding utility of the group I invention as intermediates for anticancer agents, shown in U.S. Patent No. 5,580,870 ('870) is also respectfully traversed. The compounds of group I are not disclosed, taught or suggested structurally or as useful intermediates in the '870 patent. There does not appear to be any overlap between the intermediate species of the '870 patent and the scope of structure (I). Consequently, Applicants respectfully request that the Examiner withdraw the restriction requirement, and examine both groups of claims.

A substitute specification has been provided herewith, with a new abstract and with the hydrogen atoms specified where appropriate, consistent with the Examiner's objection to the Specification on page 6, first paragraph of the Official Action.

The claims have been amended to specify that X represents CH. Applicants reserve the right to prosecute the subject matter of group II by filing additional applications as appropriate.

The Examiner rejected claims 15-16 for non-enablement, claims 1-5, 7, 9, 10 and 14-16 for indefiniteness, and claims 1, 5, 7, 10 and 14 for obviousness over Barker (U.S. Patent No. 5,580,870 ('870)). Applicants respectfully traverse.

Claims 1, 7 and 8 have been amended to clarify the language contained therein. The amended language does not constitute the improper addition of new matter. The definitions of ring A and $R^1$ have been clarified. It is noted for clarification that when the hydrogen of a hydroxyalkyl group is substituted, an alkoxyalkyl group is present.

The Examiner's comments regarding the treatment of diabetes and the treatment or prevention of obesity are respectfully traversed. The activation of the enzyme glucokinase occurs primarily in the liver and pancreatic β-cells. Glucokinase activation functions as a step in glucose metabolism. Thus, activators of the enzyme are useful due to the combined effects of enhancing glucose uptake in liver and augmenting insulin secretion from pancreatic β-cells. Both of these phenomena have been validated using animal models; and the correlation between activation of glucokinase and glucose lower has been recognized by medicinal chemists and physicians of ordinary skill in the art for several years. Applicants submit that when the state of the art is taken into account, there is no doubt that the use of glucokinase activators, such as those of the present application, is enabled. Given the content of the specification, no more than routine skill is required to make and use the compounds of claim 1 in the treatment of diabetes. Consequently, claim 15 is fully enabled.

The comments pertaining to claim 16 are likewise traversed. Treatment and prevention of obesity have been retained in the claims because a physician of ordinary skill is clearly able to determine which patients are is in need of treatment, can clearly determine whether treatment has been effective, and can clearly continue treatment after the initial weight loss to prevent relapse. Routine tests such as weighing the patient, evaluating a patient's family history from an obesity perspective, considering the patient's medical history and calculating the patient's percentage body fat would be examples of routine patient examination, and would be all that is required of the physician. None of these aspects of patient evaluation go beyond the level of ordinary skill in the medical arts.

Applicants respectfully disagree that "no known drug" can successfully prevent or reverse the course of obesity. The term "prevent" must be taken in conjunction with the rest of the claim language, in particular, with the phrase "in a mammalian patient in need of such treatment". Physicians are more than capable of determining which of their patients are "in need of such treatment" using routine levels of skill. To allege otherwise is to fail to recognize the level of routine medical skill in the ordinarily skilled physician. "Prevent" in the context of the present application need not be construed by using a general dictionary that does not relate to medicine or medicinal terminology. In fact, in Dorland's Illustrated Medical Dictionary, treatment is defined as "management and care of a patient for the purpose of combating the disease or disorder", and

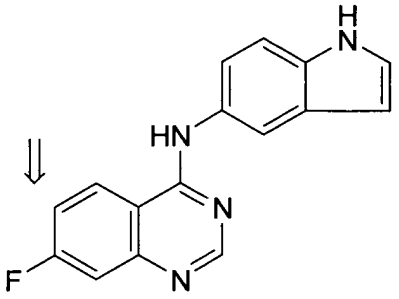
"preventive treatment" has been defined as "treatment in which the aim is to prevent the occurrence of the disease; prophylaxis". See, Dorland's Illustrated Medical Dictionary 27th ed. (1988) p. 1747.

Applicants respectfully disagree with the suggestion that "no known drug can successfully prevent or reverse the course of obesity". Obesity has been treated and prevented by physicians for decades, with different classes of drugs ranging from fat absorption blocking compounds (Xenical brand of orlistat or Alli, and cetilistat) to antidepressants (Meridia brand of sibutramine, Wellbutrin brand of bupropion) to stimulants (amphetamine, phentermine) to thyroid preparations. Applicants respectfully urge that notwithstanding the large number of unproven remedies that are available, the drugs listed above are art-recognized medicines for the treatment or prevention of obesity. Based upon the foregoing, it is urged that the rejections under 35 U.S.C. 112 have been overcome.

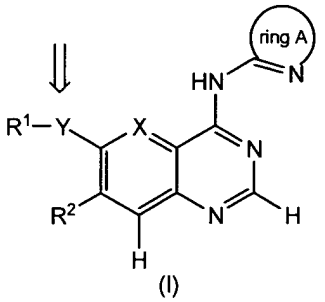
The rejection of claims 1, 5, 7, 10, and 14 for obviousness over Barker '870 is respectfully traversed. The species that were disclosed in the table of Barker '870 and relied upon by the Examiner do not contain a hydrogen or fluorine atom at position 7 of the quinazoline ring system, but rather a methoxy group. Moreover, none of the compounds disclosed in Barker '870 are alleged to have glucokinase activating activity. Instead, the compounds of Barker '870 are disclosed as tyrosine kinase receptor inhibitors, and therefore alleged to be useful as anti-cancer agents. In view of Barker '870, utility of the presently claimed compounds for the treatment of type 2 diabetes constitutes an unexpected property over Barker '870 that renders the presently claimed compounds non-obvious to those of ordinary skill in the art.

The Examiner also identified Example 21 as a position isomer of the presently claimed compounds. Please see the comparison below. The compound (Example 21) of Barker '870 is missing a substituent group, that would be equivalent to $R^1$-Y in the present genus of compounds.

EXAMPLE 21
OF BARKER




Formula I




Hence, Applicants respectfully disagree that Barker's Example 21 addresses a position isomer of the compounds of formula I. The absence of a group equivalent to $R^1$-Y- renders the compound of Example 21 patentably distinct, such that the claimed compounds are not obvious in view of Example 21.

Based upon the foregoing, prima facie obviousness of the claimed invention does not exist. Consequently, a showing of unexpected or surprising results is not required.

It is urged that all of the Examiner's rejections and reasoning in support thereof have been overcome. Consequently, reconsideration and allowance of the captioned patent application are respectfully requested. If the Examiner has any questions, she is respectfully requested to telephone the undersigned.

Respectfully submitted,

By _____
Richard C. Billups, Reg. No. 31,916
Attorney for Applicants

Merck & Co., Inc.
P.O. Box 2000
Rahway, NJ 07065-0907
(732) 594-4683

Date: August 1, 2008